

WHAT IS CLAIMED IS:

1. An immunomer, comprising at least two oligonucleotides linked at their 3' ends or  
internucleoside linkages or a functionalized nucleobase or sugar to a non-  
nucleotidic linker, wherein at least one of the oligonucleotides is an  
immunomodulatory oligonucleotide having an accessible 5' end and comprising  
an immunostimulatory dinucleotide having the structure RpG, wherein R has the  
structure shown in Figure 15 and G is selected from the group consisting of  
guanosine, 2'-deoxyguanosine, 2' deoxy-7-deazaguanosine, 2'-deoxy-6-  
thioguanosine, arabinoguanosine, 2'-deoxy-2'-substituted-arabinoguanosine, 2'-  
O-substituted-arabinoguanosine, or other non-natural purine nucleoside.
2. An immunomodulatory oligonucleotide comprising an immunostimulatory  
dinucleotide having the structure RpG, wherein R has the structure shown in  
Figure 15 and G is selected from the group consisting of guanosine,  
2'-deoxyguanosine, 2' deoxy-7-deazaguanosine, 2'-deoxy-6-thioguanosine,  
arabinoguanosine, 2'-deoxy-2'substituted-arabinoguanosine, 2'-O-substituted-  
arabinoguanosine, or other non-natural purine.
3. The immunomer according to claim 1 having the structure
- $$5'-Nn-N1-Y-Z-N1-Nn-3' \quad (III)$$

wherein:

the base of Y is 2-oxo-7-deaza-8-methyl-purine;

the base of Z is guanine, 2-amino-6-oxo-7-deazapurine, 2-amino-6-  
thiopurine, 6-oxo-purine or other non-natural purine nucleoside,

5 N1 and Nn at each occurrence, is a naturally occurring or a synthetic nucleoside or an immunostimulatory moiety selected from the group consisting of abasic nucleosides, arabinonucleosides, 2'-deoxyuridine,  $\alpha$ -deoxyribonucleosides,  $\beta$ -L-deoxyribonucleosides, and nucleosides  
10 linked by a phosphodiester or modified internucleoside linkage to the adjacent nucleoside on the 3' side, the modified internucleotide linkage being selected from, without limitation, a linker having a length of from about 2 angstroms to about 200 angstroms, C2-C18 alkyl linker, poly(ethylene glycol) linker, 2-aminobutyl-1,3-propanediol linker, glyceryl linker, 2'-5' internucleoside linkage, and phosphorothioate, phosphorodithioate, or methylphosphonate internucleoside linkage, wherein the recited oligonucleotide is directly or indirectly linked to another oligonucleotide.

4. The immunomodulatory oligonucleotide according to claim 2 having the structure  
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$$5'-Nn-N1-Y-Z-N1-Nn-3' \quad (III)$$

wherein:

the base of Y is 2-oxo-7-deaza-8-methyl-purine;

the base of Z is guanine, 2-amino-6-oxo-7-deazapurine, 2-amino-6-thiopurine, 6-oxo-purine or other non-natural purine nucleoside,

20 N1 and Nn at each occurrence, is a naturally occurring or a synthetic nucleoside or an immunostimulatory moiety selected from the group consisting of abasic nucleosides, arabinonucleosides, 2'-deoxyuridine,  $\alpha$ -deoxyribonucleosides,  $\beta$ -L-deoxyribonucleosides, and nucleosides linked by a phosphodiester or modified internucleoside linkage to the

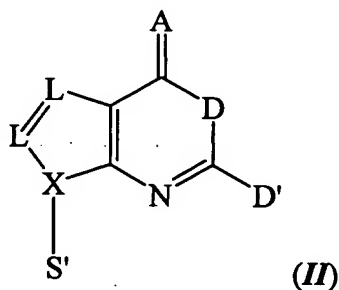
- adjacent nucleoside on the 3' side, the modified internucleotide linkage being selected from, without limitation, a linker having a length of from about 2 angstroms to about 200 angstroms, C2-C18 alkyl linker, poly(ethylene glycol) linker, 2-aminobutyl-1,3-propanediol linker, glyceryl linker, 2'-5' internucleoside linkage, and phosphorothioate, phosphorodithioate, or methylphosphonate internucleoside linkage.
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5. The immunomer according to claim 3 wherein the immunostimulatory moiety is selected from the group consisting of abasic nucleosides, arabinonucleosides, 2'-deoxyuridine,  $\alpha$ -deoxyribonucleosides,  $\beta$ -L-deoxyribonucleosides, and nucleosides linked by a modified internucleoside linkage to the adjacent nucleoside on the 3' side, the modified internucleotide linkage being selected from the group consisting of C2-C18 alkyl linker, poly(ethylene glycol) linkage, 2-aminobutyl-1,3-propanediol linker, 2'-5' internucleoside linkage, methylphosphonate internucleoside linkage; methylphosphonothioates, phosphotriesters, phosphothiotriesters, phosphorothioates, phosphorodithioates, triester prodrugs, sulfones, sulfonamides, sulfamates, formacetal, N-methylhydroxylamine, carbonate, carbamate, morpholino, boranophosphonate, phosphoramidates, especially primary amino-phosphoramidates, N3 phosphoramidates and N5 phosphoramidates, and stereospecific linkages, nucleosides having sugar modifications, 2'-substituted pentose sugars including, without limitation, 2'-O-methylribose, 2'-O-methoxyethylribose, 2'-O-propargylribose, and 2'-deoxy-2'-fluororibose; 3'-substituted pentose sugars, including, without limitation, 3'-O-methylribose; 1',2'-dideoxyribose; arabinose; substituted arabinose sugars, hexose sugars, and alpha-anomers, peptide nucleic acids (PNA), peptide nucleic acids with phosphate groups (PHONA), locked nucleic acids (LNA), morpholinonucleic acids, and oligonucleotides having backbone linker sections having a length of from about 2 angstroms to about 200 angstroms, alkyl
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linkers or amino linkers, DNA isoforms,  $\beta$ -L-deoxyribonucleosides,  $\alpha$ -deoxyribonucleosides, nucleosides having unnatural internucleoside linkage positions, and nucleosides having modified heterocyclic bases.

- 5 6. The immunomodulatory oligonucleotide according to claim 4, wherein the immunostimulatory moiety is selected from the group consisting of abasic nucleosides, arabinonucleosides, 2'-deoxyuridine,  $\alpha$ -deoxyribonucleosides,  $\beta$ -L-deoxyribonucleosides, and nucleosides linked by a modified internucleoside linkage to the adjacent nucleoside on the 3' side, the modified internucleotide linkage being selected from the group consisting of C2-C18 alkyl linker, 10 poly(ethylene glycol) linkage, 2-aminobutyl-1,3-propanediol linker, 2'-5' internucleoside linkage, methylphosphonate internucleoside linkage; methylphosphonothioates, phosphotriesters, phosphothiotriesters, phosphorothioates, phosphorodithioates, triester prodrugs, sulfones, sulfonamides, sulfamates, formacetal, N-methylhydroxylamine, carbonate, carbamate, 15 morpholino, boranophosphonate, phosphoramidates, especially primary amino-phosphoramidates, N3 phosphoramidates and N5 phosphoramidates, and stereospecific linkages, nucleosides having sugar modifications, 2'-substituted pentose sugars including, without limitation, 2'-O-methylribose, 2'-O-methoxyethylribose, 2'-O-propargylribose, and 2'-deoxy-2'-fluororibose; 20 3'-substituted pentose sugars, including, without limitation, 3'-O-methylribose; 1',2'-dideoxyribose; arabinose; substituted arabinose sugars, hexose sugars, and alpha-anomers, peptide nucleic acids (PNA), peptide nucleic acids with phosphate groups (PHONA), locked nucleic acids (LNA), morpholinonucleic acids, and oligonucleotides having backbone linker sections having a length of from about 2 25 angstroms to about 200 angstroms, alkyl linkers or amino linkers, DNA isoforms,  $\beta$ -L-deoxyribonucleosides,  $\alpha$ -deoxyribonucleosides, nucleosides having

unnatural internucleoside linkage positions, and nucleosides having modified heterocyclic bases.

7. The immunomer of claim 1 wherein the immunomer comprises at least one oligonucleotide that is complementary to a gene.
- 5 8. The immunomer of claim 1 wherein the immunomer comprises at least one ribozyme or a decoy oligonucleotide.
9. The immunomer of claim 1 wherein the immunomer comprises at least one Nn portion that includes a G3-G10 region.
- 10 10. The immunomer according to claim 1 wherein one purine nucleoside in the immunostimulatory dinucleotide has the structure (II):



wherein:

D is a hydrogen bond donor;

15 D' is selected from the group consisting of hydrogen, hydrogen bond donor, and hydrophilic group;

A is a hydrogen bond acceptor or a hydrophilic group;

X is carbon or nitrogen;

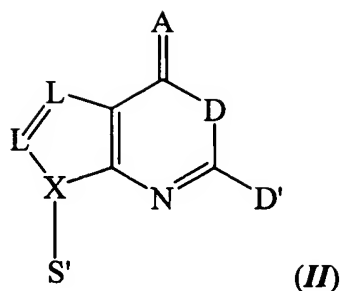
each L is independently an atom selected from the group consisting of C, O, N and S; and

S' is a pentose or hexose sugar ring, or a non-naturally occurring sugar.

11. The immunomer according to claim 10 wherein the sugar ring is derivatized with a phosphate moiety, modified phosphate moiety, or other linker moiety suitable for linking the purine nucleoside to another nucleoside or nucleoside analog.
12. The immunomer according to claim 10 wherein the hydrogen bond donors are selected from the group consisting of -NH-, -NH<sub>2</sub>, -SH and -OH.
13. The immunomer according to claim 10 wherein the hydrogen bond acceptors are selected from the group consisting of C=O, C=S, -N= and the ring nitrogen atoms of an aromatic heterocycle.
14. The immunomer according to claim 10 wherein the non-naturally occurring purine is 2-amino-6-thiopurine, 6-oxopurine or 2-amino-6-oxo-7-deazapurine.
15. The immunomer according to claim 1, wherein the non-nucleotidic linker is selected from the group consisting of a linker from about 2 angstroms to about 200 angstroms in length, a metal, a soluble or insoluble biodegradable polymer bead, an organic moiety having functional groups that permit attachment to the 3'-terminal nucleoside of the oligonucleotide, a biomolecule, a cyclic or acyclic small molecule, an aliphatic or aromatic hydrocarbon, either of which optionally can include, either in the linear chain connecting the oligonucleotides or appended to it, one or more functional groups selected from the group consisting of hydroxy, amino, thiol, thioether, ether, amide, thioamide, ester, urea, and thiourea; amino acids, carbohydrates, cyclodextrins, adamantane, cholesterol, haptens antibiotics, glycerol or a glycerol homolog of the formula

HO-(CH<sub>2</sub>)<sub>o</sub>-CH(OH)-(CH<sub>2</sub>)<sub>p</sub>-OH, wherein *o* and *p* independently are integers from 1 to about 6, and a derivative of 1,3-diamino-2-hydroxypropane.

16. The immunomer according to claim 1, wherein the internucleoside linkages consist essentially of phosphodiester linkages.
- 5 17. An immunomer conjugate, comprising an immunomer, according to claim 1 and an antigen conjugated to the immunomer at a position other than the accessible 5' end.
- 18 18. The immunomer according to claim 1, wherein G is arabinoguanosine or 2'-deoxy-2'-substituted arabinguanosine, 2'-deoxy-7-deazaguanosine or 2'-deoxy-6-10 thioguanosine, or 2'-deoxyinosine.
19. The immunomodulatory oligonucleotide of claim 2 wherein the oligonucleotide is complementary to a gene.
20. The immunomodulatory oligonucleotide of claim 2 wherein the oligonucleotide comprises a ribozyme or a decoy oligonucleotide.
- 15 21. The immunomodulatory oligonucleotide of claim 2 comprising at least one Nn portion that includes a G3-G10 region.
22. The immunomodulatory oligonucleotide according to claim 2 wherein one purine nucleoside in the immunostimulatory dinucleotide has the structure (*II*):



wherein:

D is a hydrogen bond donor;

5 D' is selected from the group consisting of hydrogen, hydrogen bond donor, and hydrophilic group;

A is a hydrogen bond acceptor or a hydrophilic group;

X is carbon or nitrogen;

each L is independently an atom selected from the group consisting of C, O, N and S; and

10 S' is a pentose or hexose sugar ring, or a non-naturally occurring sugar.

23. The immunomodulatory oligonucleotide according to claim 22 wherein the sugar ring is derivatized with a phosphate moiety, modified phosphate moiety, or other linker moiety suitable for linking the purine nucleoside to another nucleoside or nucleoside analog.

15 24. The immunomodulatory oligonucleotide according to claim 22 wherein the hydrogen bond donors are selected from the group consisting of -NH-, -NH<sub>2</sub>, -SH and -OH.



25. The immunomodulatory oligonucleotide according to claim 22 wherein the hydrogen bond acceptors are selected from the group consisting of C=O, C=S, -N= and the ring nitrogen atoms of an aromatic heterocycle.
- 5 26. The immunomodulatory oligonucleotide according to claim 22 wherein the non-naturally occurring purine is 2-amino-6-thiopurine or 2-amino-6-oxo-7-deazapurine.
- 10 27. The immunomodulatory oligonucleotide according to claim 2, wherein the non-nucleotidic linker is selected from the group consisting of a linker from about 2 angstroms to about 200 angstroms in length, a metal, a soluble or insoluble biodegradable polymer bead, an organic moiety having functional groups that permit attachment to the 3'-terminal nucleoside of the oligonucleotide, a biomolecule, a cyclic or acyclic small molecule, an aliphatic or aromatic hydrocarbon, either of which optionally can include, either in the linear chain connecting the oligonucleotides or appended to it, one or more functional groups selected from the group consisting of hydroxy, amino, thiol, thioether, ether, amide, thioamide, ester, urea, and thiourea; amino acids, carbohydrates, cyclodextrins, adamantane, cholesterol, haptens antibiotics, glycerol or a glycerol homolog of the formula  $\text{HO}-(\text{CH}_2)_o-\text{CH}(\text{OH})-(\text{CH}_2)_p-\text{OH}$ , wherein  $o$  and  $p$  independently are integers from 1 to about 6, and a derivative of 1,3-diamino-2-hydroxypropane.
- 15 28. The immunomodulatory oligonucleotide according to claim 2, wherein the internucleoside linkages consist essentially of phosphodiester linkages.
- 20 29. An immunomodulatory oligonucleotide conjugate, comprising an immunomodulatory oligonucleotide according to claim 2 and an antigen conjugated to the immunomer at a position other than the accessible 5' end.
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30. The immunomodulatory oligonucleotide according to claim 2, wherein G is arabinoguanosine or 2'-deoxy-2'-substituted arabinguanosine, 2'-deoxy-7-deazaguanosine or 2'-deoxy-6-thioguanosine, or 2'-deoxyinosine.
- 5 31. A pharmaceutical formulation comprising an immunomer according to claim 1 and a physiologically acceptable carrier.
32. A method for generating an immune response in a vertebrate, the method comprising administering to the vertebrate an immunomer according to claim 1.
- 10 33. A method for generating an immune response in a vertebrate, the method comprising administering to the vertebrate an immunomer conjugate according to claim 17.
34. A method for therapeutically treating a patient having a disease or disorder, such method comprising administering to the patient an immunomer according to claim 1.
- 15 35. The method according to claim 34 wherein the disease or disorder to be treated is cancer, an autoimmune disorder, airway inflammation, inflammatory disorders, skin disorders, allergy, asthma or a disease caused by a pathogen.
36. A method for therapeutically treating a patient having a disease or disorder, such method comprising administering to the patient an immunomer conjugate according to claim 17.
- 20 37. A method for therapeutically treating a patient having a disease or disorder, such method comprising administering to the patient an immunomer according to claim 10.

38. The method according to claim 36 wherein the disease or disorder to be treated is cancer, an autoimmune disorder, airway inflammation, allergy, asthma or a disease caused by a pathogen.
- 5 39. The method according to claim 37 wherein the disease or disorder to be treated is cancer, an autoimmune disorder, airway inflammation, allergy, asthma or a disease caused by a pathogen.
40. The method of claim 32 further comprising administering a vaccine.
41. The method of claim 40, wherein the immunomer or the vaccine, or both, are linked to an immunogenic protein.
- 10 42. The method of claim 40 further comprising administering an adjuvant.
43. A method for generating an immune response in a vertebrate, the method comprising administering to the vertebrate an immunomodulatory oligonucleotide according to claim 2.
- 15 44. A method for generating an immune response in a vertebrate, the method comprising administering to the vertebrate an immunomodulatory oligonucleotide conjugate according to claim 29.
45. A method for therapeutically treating a patient having a disease or disorder, such method comprising administering to the patient an an immunomodulatory oligonucleotide according to claim 4.
- 20 46. The method according to claim 45 wherein the disease or disorder to be treated is cancer, an autoimmune disorder, airway inflammation, inflammatory disorders, skin disorders, allergy, asthma or a disease caused by a pathogen.

47. A method for therapeutically treating a patient having a disease or disorder, such method comprising administering to the patient an immunomodulatory oligonucleotide conjugate according to claim 29.
- 5 48. A method for therapeutically treating a patient having a disease or disorder, such method comprising administering to the patient an immunomodulatory oligonucleotide according to claim 22.
49. The method according to claim 47 wherein the disease or disorder to be treated is cancer, an autoimmune disorder, airway inflammation, allergy, asthma or a disease caused by a pathogen.
- 10 50. The method according to claim 48 wherein the disease or disorder to be treated is cancer, an autoimmune disorder, airway inflammation, allergy, asthma or a disease caused by a pathogen.
51. The method of claim 44 further comprising administering a vaccine.
52. The method of claim 51, wherein the immunomer or the vaccine, or both, are  
15 linked to an immunogenic protein.
53. The method of claim 44 further comprising administering an adjuvant.
54. The method according to claim 48, further comprising administering another therapeutic agent.
- 20 55. The method according to claim 54, wherein the other therapeutic agent is selected from the group consisting of vaccines, antibodies, allergens, antibiotics and chemotherapeutic agents.

56. An immunostimulatory oligonucleotide comprising two or more oligonucleotide segments covalently linked 5' to 3' by a non-nucleotidic linker.